American Journal of Epidemiology
Vol. 151, No. 1
Printed in U.S.A.


## INSTRUCTIONS TO AUTHORS OF HuGE REVIEWS

# Revised Guidelines For Submitting HuGE Reviews

We invite authors to submit HuGE reviews to the *American Journal of Epidemiology*, *Epidemiologic Reviews*, or one of the collaborating journals listed on the HuGE Net website (http://www.cdc.gov/genetics/hugenet/default.htm). These submissions will be peer-reviewed and, if accepted, will be published in one of these journals as well as in the HuGE Net knowledge base on the World Wide Web. The suggested revised format for a HuGE review is outlined below. The topics of these reviews can range from genetic variants or mutations associated with high disease risks (e.g., cystic fibrosis) to polymorphisms and normal variants (such as apolipoprotein E-E4) associated with variable disease risks. In the case of genes associated with multiple disease outcomes (e.g., *BRCA1* and breast cancer and ovarian cancer), HuGE review authors may elect to restrict their reviews to one or more disease entities as long as they acknowledge the association with other diseases. In addition, when multiple gene variants are associated with different diseases, reviewers may focus on one or more of these variants in relation to one or more diseases (e.g., apolipoprotein E-E4 allele and Alzheimer's disease). Authors should acknowledge the presence of other gene variants (e.g., apoliprotein E-E3 or E2) and the association with other diseases (e.g., coronary heart disease).

The objective of a HuGE review is to identify a gene's allelic variants and describe what is known about the frequency of these variants in different populations, to identify diseases with which these variants are associated, and to summarize the magnitude of risks and associated risk factors. A crucial component of a HuGE review is to identify gaps in the epidemiologic knowledge base for human gene variants in order to stimulate further work in these areas. We expect these reviews to be concise (5,000 words or fewer, excluding tables and references). Authors are to describe the sources of information they searched, their criteria for including some papers and excluding others, and their criteria for evaluating the quality of publications and the methods they used to summarize data and draw conclusions. Tables and figures are welcome for the purpose of summarizing and evaluating the quality of epidemiologic information. We expect authors to provide up-to-date references. We also expect relevant links to World Wide Web resources, including genetics databases, online resources, educational materials, consensus statements, policy statements, and support groups.

If you are interested in submitting a HuGE review, please send an electronic message of your intent to the HuGE Net coordinator at genetics@cdc.gov to sign up for a HuGE review. A review is due within 6 months. An updated list of HuGE reviews under development is kept on the HuGE Net website at www.cdc.gov/genetics. This is crucial to keeping track of HuGE reviews under development and avoiding potential duplication and overlap. The HuGE Net coordinator may suggest collaboration with other authors when proposed HuGE reviews overlap, e.g., in the preparation of the section Gene variants. The HuGE Net coordinator will advise about which journal will be the most appropriate for the proposed review topic. Authors should then submit completed HuGE reviews to the editor of the appropriate journal, with a cover letter explaining that the manuscript is for consideration as a HuGE review and suggesting the names of up to three possible reviewers. The technical requirements of each journal for submission of manuscripts should be followed. Because of space constraints, it may not be possible for a journal to publish all of the tables and references prepared for a HuGE review. It is expected that the text of a HuGE review in a journal and that available on the HuGE Net website will be identical and that reference would be made to the additional tables and references held on the website. Accepted papers will be published both in the appropriate journal and on the HuGE Net website.

### FORMATS FOR HUGE REVIEWS

There are two main formats for a HuGE review. First, a full review is needed the first time the epidemiologic aspects of a specific gene are reviewed for HuGE Net. Second, a minireview may be appropriate when the epidemiologic aspects of a specific gene have already been reviewed for HuGE Net, but the associations between the gene and a different disease are being reviewed.

### FORMAT FOR FULL REVIEWS

#### Abstract

Provide a one-page synopsis of the issues discussed in the items below with a brief statement on each of

these items. Supply keywords, including the name(s) of the gene(s), the name(s) of the disease(s) or disorder(s), and the word "epidemiology."

### Gene

Identify the gene being reviewed and provide a brief review of its chromosome location, the gene product, and its function, if known.

### Gene variants

List known allelic variants and summarize known information on the frequency of homozygosity and heterozygosity of these variants in different populations and ethnic groups. The strategy used to identify relevant papers should be specified, including the databases searched and the period of publication considered. Brief details of any hand searches should be given. The summary of variation in genotype frequency should include a table and a commentary on this in the text. The date of preparation of the table should be indicated in a footnote on each page. It is recommended that the following information be included:

*Geographic area in which the study was carried out.* Provide a brief description of how the subjects whose genotypes were determined were sampled, e.g., subjects selected randomly from a population-based sampling frame, blood donors, hospitalized subjects (give reasons). When possible, the description should include the mean age (standard deviation) or age range and the distribution by gender. If the subjects were controls from a case-control study, the disease under investigation and any matching criteria should be specified (e.g., subjects matched to lung cancer patients on age, sex, and smoking history). When relevant, the ethnic group should be specified.

If genotyping in a substantial proportion of studies was inferred on the basis of phenotypic tests, these studies should be grouped in a specific section of the table. If more than one type of test was used, a column should be used to indicate the type of test used in the study.

*Number of subjects whose genotypes were determined.* When there are multiple alleles, those tested for should be specified.

*Genotype frequency, with 95 percent confidence interval.* Whenever possible, genotype frequency should be presented in preference to allele frequencies. For two allele systems, when it is firmly established that heterozygotes and homozygotes for the common allele have similar enzyme levels, it is sufficient to present the frequency of homozygotes for the variant allele. When genotype-enzyme level relations are not well established, we suggest presenting the frequency of homozygotes for the variant allele and heterozygotes in separate columns.

For multiple allele systems, when genotype-enzyme level relations are well established, grouping may be made on the basis of inferred phenotype. When genotype-enzyme level relations are not well established, we suggest presenting the frequencies of homozygotes for the most common variant. Inclusion of frequencies of other genotypes will depend on the range of alleles investigated in the studies included in the review.

The in-text reference should be specified in the following format: single author—last name, year of publication (reference number); two authors—last name 1 and last name 2, year of publication (reference number); more than two authors—last name et al., year of publication (reference number).

It is suggested that order of the articles reviewed be first by continent or major geographic area (e.g., Americas, Africa, Asia, Europe, Oceania) and then alphabetically by location within country (multicenter studies and studies in which the location within the country is not specified first). This order makes it relatively easy to see sequential publications relating to the same population.

### Disease(s)

Identify the disease(s) or disorder(s) with which this gene is associated. Briefly summarize the descriptive epidemiology and confirmed and suspected risk factors (including other genes).

### Associations

As it is likely that the search strategy will have been similar to that for the distribution of the relevant genotypes in different populations and ethnic groups, it will normally be sufficient to cross-refer to the strategy described in the section Gene variants and state what additional headings and text words relevant to the disease or disorder have been added. Summarize the magnitude of the association between the allelic variants and various diseases in terms of absolute, relative, and attributable risks in different populations. Comment on the quality and methodology of studies. Especially for studies of the association between genetic polymorphisms postulated to affect susceptibility, it may be helpful to summarize the studies in a table in the following format:

*Geographic area in which the study was carried out and period of recruitment of study subjects.*

*Case type and number.* The type should include the condition under investigation (so that differences between studies can be identified), the method of ascer-

tainment (e.g., register, one hospital, several hospitals, family practitioners), age range, gender distribution, and, if available, participation rate. If a nested case-control or case cohort design was used, this should be specified.

*Controls (or cohort) type and number.* Sufficient information should be given for the reader to understand whether cases and controls were derived from the same source population, with similar eligibility criteria, and whether matching was carried out. (If matching was used, the matching variables should be specified).

For loci for which there are multiple alleles, the alleles investigated and the comparison to which the relative risk estimate relates should be specified. It is possible that ad hoc calculations will have to be made from the information presented to enable comparison between studies. When this has been done, it should be noted, e.g., by enclosing the relative risk in square brackets.

When the studies of genotype-disease associations have been carried out in a limited number of geographic areas or if selection bias is thought to be an issue in the interpretation of these studies, it may be helpful to include a column specifying the population of controls with the genotype to which the primary hypothesis relates.

*Relative risk and 95 percent confidence interval for the stated comparison.* When adjustment has been carried out, these should be specified. When no estimate is presented and insufficient data are presented for calculation, but the authors have commented on an association, this should be stated.

For some genotype-disease associations, subgroup analyses have been reported. So far, the statistical power of many of these analyses has been low. It may be helpful to include a column indicating what subgroups have been analyzed (e.g., subsite of tumor, tumor histology, age, ethnic group), but discuss the results in the text rather than trying to summarize all subgroup analyses in a table.

Brief details of any exposure assessment carried out to investigate possible interaction (effect modification) should be included.

*The results of any analysis of possible interaction (effect modification) should be summarized..* The in-text reference should be specified in the format already described.

### Interactions

Discuss whether the allelic variants interact with any of the disease known risk factors, including other genes and environmental factors. Summarize the magnitude of such interactions.

### Laboratory tests

Summarize the sensitivity, specificity, and positive and negative predictive values (including 95 percent confidence intervals) of different tests available for the gene, including biochemical, molecular, and other tests in different populations. Summarize the type of study subjects in which the analytic or clinical validity of the tests were investigated.

### Population testing

Summarize population-specific data on the magnitude and determinants of testing for allelic variants of this gene and the impact of testing on public health (morbidity, mortality, disability), including policy statements, recommendations, and legislation (including mention of available interventions). This section should include a table summarizing the quality of evidence regarding population testing and any associated intervention that might affect the relation between the gene and the disease. The table and brief accompanying text should identify gaps in the evidence base regarding the public health implications of human gene variants in order to stimulate work to fill these gaps.

### References (according to journal format)

### Internet sites

Include relevant links to various genetics databases, online resources, educational materials, consensus statements, policy statements, and support groups.

The suggested format for a mini-HuGE review is similar to that of the full review with the exception of the following: Under the section Gene variants, authors should provide only a brief summary of the points covered in the full review(s) relating to this gene, with appropriate cross-referencing. Under the section Disease(s), if the disease has been considered in another HuGE review, cross-reference to this should be made. Identify the disease(s) or disorders with which this gene is associated. Briefly summarize the descriptive epidemiology and confirmed and suspected risk factors (including other genes).